DETAILED ACTION

1. Claims 1-10 are pending.

Claim Objections

2. Claim 5 is objected to because of the following informalities:

> 5. The process of claim 1 wherein the part or device comprises a tissue engineering device and printing in step (d) involves direct deposition of cells or biological factors.

There is no limitation "d" in claim 1. It is interpreted that this refers to limitation "c". Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim limitation is ambiguous enough to include the interpretation that 'simultaneous' refers to simultaneously depositing at the exact same place at the same exact time. This does not appear to be possible. It is interpreted that the claim refers to simultaneously depositing at different locations; however, the rejection is asserted until the issue is resolved.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites:

> simultaneously depositing specified hydrogels with different viscosities thereby constructing a scaffold from the designed scaffold model.

However, it is not clear whether simultaneous refers to simultaneously depositing at the same place, which does not appear to be possible, or to simultaneously depositing at different locations. It is interpreted that the claim refers to simultaneously depositing at different locations.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1-9 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Mironov et al.(applicant's IDS of 10/26/2007).

9. Mironov et al. disclose:

> 1. A process for manufacturing complex parts and devices comprising:
>
> (a) utilizing a CAD environment to design a part or device to be created;
>
> (b) converting the CAD designed part or device into a heterogeneous material and multi-part assembly model which can be used for multi-nozzle

printing; and

(c) printing the designed part or device using multiple, different, specialized nozzles.

See title: Organ printing: computer-aided jet-based 3D tissue engineering

See first paragraph, page 157:

Tissue engineering technology promises to solve the organ transplantation crisis. However, assembly of vascularized 3D soft organs remains a big challenge. Organ printing, which we define as computer-aided, jetbased 3D tissue-engineering of living human organs, offers a possible solution. Organ printing involves three sequential steps: pre-processing or development of 'blueprints' for organs; processing or actual organ printing; and postprocessing or organ conditioning and accelerated organ maturation. A cell printer that can print gels, single cells and cell aggregates has been developed. Layer-by-layer sequentially placed and solidified thin layers of a thermo-reversible gel could serve as 'printing paper'. Combination of an engineering approach with the developmental biology concept of embryonic tissue fluidity enables the creation of a new rapid prototyping 3D organ printing technology, which will dramatically accelerate and optimize tissue and organ assembly.

Page 159 - col. 1:

What is organ printing?

Organ printing is a biomedically relevant variant of rapid prototyping technology, which is based on tissue fluidity. Computer-assisted deposition ('printing') of natural materials (cells or matrix) is done one layer at time until a particular 3D form is achieved. However, recent attempts using rapid prototyping technologies to design **solid synthetic scaffolds** [12-15] suffer from the inability to precisely place cells or cell aggregates into a printed scaffold. Thus, we believe that organ-printing technology will become increasingly more 'secondum naturam'.We define organ printing as a rapid prototyping computer-aided 3D printing technology, based on using layer by layer **deposition of cell and/or cell aggregates** into a 3D gel with sequential maturation of the printed construct into perfused and vascularized living tissue or organ (Figs 2-4). This definition of organ printing includes the many different printer designs and components of the deposition process such as, for example, jet-based cell printers, cell dispensors or bioplotters, the different types of 3D hydrogels and varying cell types.

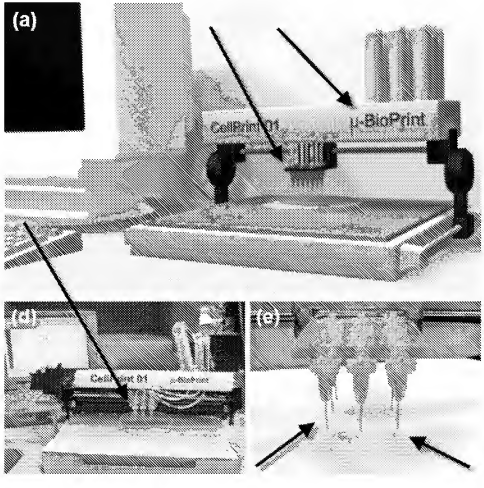
And

Page 159 - col. 2:

The procedure of organ printing can be subdivided into three sequential steps: preprocessing, processing and postprocessing. Preprocessing primarily deals with the development of a computer-aided design (CAD) or blueprint of a specific organ. The design can be derived from digitized image reconstruction of a natural organ or tissue. Imaging data can be derived from various modalities including noninvasive

scanning of the human body (e.g. MRI or computerized tomography) or a detailed 3D reconstruction of serial sections of specific organs (see [16] for a recent review). Yet another approach to designing a tissue is based on mathematical modeling using a set of theoretical principles, rules or laws related to spatial organization. One the most impressive recent examples of this technology is called 'constrained constructed optimization' (CCO), which was developed by Karch et al. [17]. Processing usually refers to actual computer-aided printing or layer by-layer placement of cells or cell aggregates into a 3D environment using CAD or blueprints. Finally, postprocessing is concerned with the perfusion of printed organs and their biomechanical conditioning to both direct and accelerate organ maturation.

See fig. 2:



2. The process of claim 1 further comprising using Boolean, scaling, smoothing, mirroring, or other operations to modify the CAD design prior to conversion into a heterogeneous material and multi-part assembly model.

Page 159 - col. 2:

> The procedure of organ printing can be subdivided into three sequential steps: **preprocessing**, processing and postprocessing. Preprocessing primarily deals with the development of a computer-aided design (CAD) or blueprint of a specific organ. The design can be derived from digitized image reconstruction of a natural organ or tissue. Imaging data can be derived from various modalities including noninvasive scanning of the human body (e.g. MRI or computerized tomography) or a detailed 3D reconstruction of serial sections of specific organs (see [16] for a recent review).

3. The process of claim 1 wherein in step (a) data taken from MRI, CT or other patient specific data is imported into the CAD environment to design the part or device to be created.

Page 159 - col. 2:

> The procedure of organ printing can be subdivided into three sequential steps: preprocessing, processing and postprocessing. Preprocessing primarily deals with the development of a computer-aided design (CAD) or blueprint of a specific organ. The design can be derived from digitized image reconstruction of a natural organ or tissue. Imaging data can be derived from various modalities including noninvasive scanning of the human body (e.g. **MRI or computerized tomography**) or a detailed 3D reconstruction of serial sections of specific organs (see [16] for a recent review).

4. The process of claim 1 wherein a biomimetic and non-biomimetic feature is designed into the part or device.

Note that plainly stated biomimetics refers to human-made processes, substances, devices, or systems that imitate nature (mimetic: Late Latin *mimeticus,* from Greek *mimētikos,* from *mimeisthai* to imitate, from *mimos* mime; from Gk. *Bio-*, comb. form of *bios* "life, course or way of living"). The non-biomimetic scaffold is used to grow the biomemtic (cells/organ) portion. See 159 (col. 1):

> What is organ printing?
> Organ printing is a biomedically relevant variant of rapid prototyping technology, which is based on tissue fluidity. Computer-assisted deposition ('printing') of natural materials (cells or matrix) is done one layer at time until a particular 3D form is achieved. However, recent attempts using rapid prototyping technologies to design **solid synthetic scaffolds** [12–15] suffer from the inability to precisely place cells or cell aggregates into a printed scaffold. Thus, we believe that organ-printing technology will become increasingly more 'secondum naturam'.We define organ printing as a rapid prototyping computer-aided 3D printing technology, based on using layer by layer **deposition of cell and/or cell aggregates** into a 3D gel with sequential maturation of the printed construct into perfused and vascularized living tissue or organ (Figs 2–4). This definition of organ printing includes the many different printer designs and components of the deposition process such as, for example, jet-based cell printers, cell dispensors or bioplotters, the different types of 3D hydrogels and varying cell types.

5. The process of claim 1 wherein the part or device comprises a tissue engineering device and printing in step (d) involves direct deposition of cells or biological factors.
(it is interpreted that this refers to limitation "c" in so far as there is no limitation "d"). Page 159 - col. 1:

What is organ printing?
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6. The process of claim 5 wherein direct cell deposition improves histological accuracy, cell ratios, and spatial patterning of cells in the part or device.
The limitation is directed to a subjective test and furthermore refers to an intended use (intended benefit). Regardless, see abstract:
Tissue engineering technology promises to solve the organ transplantation crisis. However, assembly of vascularized 3D soft organs remains a big challenge. Organ printing, which we define as computer-aided, jet based 3D tissue-engineering of living human organs, offers a possible solution. Organ printing involves three sequential steps: pre-processing or development of 'blueprints' for organs; processing or actual organ printing; and postprocessing or organ conditioning and accelerated organ maturation. A cell printer that can print gels, single cells and cell aggregates has been developed. Layer-by-layer sequentially placed and solidified thin layers of a thermo-reversible gel could serve as 'printing paper'. Combination of an engineering approach with the developmental biology concept of embryonic tissue fluidity enables the creation of a new rapid prototyping 3D organ printing technology, **which will dramatically accelerate and optimize tissue and organ assembly**.

7. The process of claim 1 wherein the part or device produced comprises an artificial organ, a tissue scaffold, an artificial vasculature or channel system, or a sample for cytotoxicity testing.
See title: Organ printing: computer-aided jet-based 3D tissue engineering

8. The process of claim 1 wherein the part or device produced comprises a biochip, biosensor, bionic, cybernetic, mechanoactive, or a bioactive tissue scaffold.

Page 159 - col. 1:

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9. The process of claim 1 wherein the part or device is **used** in drug delivery.
Intended use - no patentable weight. The claims are directed to a process for manufacturing complex parts and devices. Regardless, see conclusion:
Besides their obvious application for organ transplantation, 3D perfused, vascularized, printed human tissues (or structural functional units of human organs) could become popular screening assays for drug discovery and testing and further biomedical research. It is safe to predict that in the 21st century, cell and organ printers will be as broadly used as biomedical research tools as was the electron microscope in the 20th century.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mironov et al. in view of Vozzi et al. (2003).

13. Mironov et al. disclose:

10. A multi-nozzle biopolymer deposition apparatus comprising:

(a) a data processing system which processes a designed scaffold model
and converts it into a layered process tool path;

(b) a motion control system driven by the layered process tool

path:

See title: Organ printing: computer-aided jet-based 3D tissue engineering

See first paragraph, page 157:
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Page 159 - col. 2:
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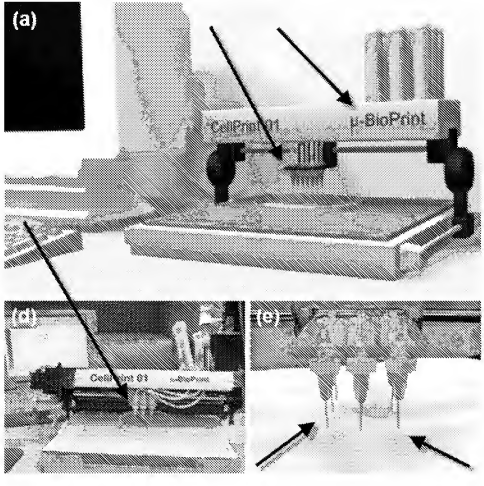

(c) a material delivery system comprising multiple nozzles of different types and sizes *for simultaneously depositing specified hydrogels with different viscosities thereby constructing a scaffold from the designed scaffold model.*

Intended use after "for" - no patentable weight. The claims are directed to a multi-nozzle biopolymer deposition apparatus.

14. Mironov et al. disclose the multiple nozzle technology as discussed but do not expressly state that the nozzles are of different types/sizes.

15. Vozzi disclose:

3.1. Microsyringe

We sought to characterize the fluidic polymer deposition of the microsyringe system. Our model predictions [26] indicate that the width of the pattern can be controlled by a number of factors which include the diameter of the tip, the viscosity of the polymer solution, the applied pressure, and the motor speed. Fig. 3a is an example of the measured relationship between the width of the pattern and the applied pressure for a fixed concentration of PLGA (20%), and a motor speed of 2.5 mm/s. Highly viscous solutions result in the highest pattern resolutions. However, solution viscosities greater than about 300 cp demand high driving pressures to extrude the liquid which may break the tip. Furthermore, highly concentrated solutions evaporate rapidly and plug the tip. For this study, 10 μm structures were deposited at 200 mm Hg using a 20% PLGA solution. Under these optimal conditions, the vertical resolution was found to be about 5–10 μm as shown by SEM analysis. The profile of the structures, which was also measured with an atomic force microscope [26], is not uniform but resembles an elliptical arc with a high aspect ratio. Multilayer structures were fabricated by depositing polymer in successive layers. Figs. 3b and c show a single layer and multilayer structure, respectively.

However, as known in the art, the high pressures may cause damage to the cellular materials. Thus, to achieve both resolution for the scaffolding and to minimize damage to the cellular materials, it would be advantageous to use at least two different sized nozzles in the nozzle array of Mironov et al.

Response to Arguments

16. Applicant's arguments, filed 5/22/2008, have been carefully considered and are not persuasive.

17. Applicant's statement in the first paragraph of page 4 is accurate. The Examiner apologizes for the typo.

18. Applicants are thanked for their interview summary.

19. Applicants arguments regarding the art are moot in view of the new art rejection.

Conclusion

20. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 10/26/2007 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

21. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be:

directed to: Dr. Hugh Jones telephone number (571) 272-3781,

Monday-Thursday 0830 to 0700 ET,

or

the examiner's supervisor, Kamini Shah, telephone number (571) 272-2279.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, telephone number (703) 305-3900.

mailed to:

Commissioner of Patents and Trademarks

Washington, D.C. 20231

or faxed to:

(703) 308-9051 (for formal communications intended for entry)

or (703) 308-1396 (for informal or draft communications, please label *PROPOSED* or *DRAFT*).

/Hugh Jones/

Primary Examiner, Art Unit 2128

September 3, 2008